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News Letter

Carbapenem-Resistant *Klebsiella pneumoniae*: Global Emergence

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Klebsiella pneumonia (*K. pneumonia*) is an important gram-negative pathogenic organism affiliated with the *Enterobacteriaceae* family that is the fourth and fifth most common cause of pneumonia and bacteremia in many healthcare settings, respectively. This gram-negative pathogen survives and multiply in wet environmental sites and colonizes in the upper respiratory tract, urinary bladder, intestine, and skin. Carbapenems, one of the "last resort antimicrobials" were often used to treat adverse infections caused by AmpC beta-lactamases (AmpCBLs) or extended-spectrum beta-lactamases (ESBLs) carrying pathogens. In 1996, *K. pneumoniae* carbapenemases, some of the epidemiologically important carbapenemases (*K. pneumoniae* carbapenemases (KPCs)) was first detected in North Carolina, USA (KPC class A enzyme). Later, it was detected in outbreak of the USA and was soon identified in South America, many European countries (2005 - 2006), and around the world. In 1990s, plasmid encoded bla_{IMP-1} and bla_{KPC-1} were reported and confirmed the presence of these carbapenem-resistant genes in mobile genetic elements that indicates potential for resistance transmission via horizontal gene transfer. Production of KPC enzymes is the most common mechanism of carbapenem-resistance among carbapenemase-producing *Enterobacteriaceae*, whereas these enzymes are most commonly detected among K. pneumoniae isolates. Production of KPC enzymes and metallo-beta-lactamases (MBLs) have become the more prevalent mechanisms for carbapenem-resistant *K. pneumoniae* (CR-KP). During 2001 to 2011, the highest increase in proportion from 1.6 % to 10.4 % was demonstrated for *Klebsiella* species according to the previous data from the United States Centers for Disease Control and Prevention. During the same period, percentage of carbapenemase-producing *Enterobacteriaceae* increased from 1.2 % to 4.2 %. ESBLs are classified into different classes (A, B, and D) on the basis of amino acid sequence homology. Class A and D carbapenemases have serine at their active site, while class B use zinc. KPC-producing strains spread in a clonal fashion, with the main isolates in the United States and European countries are belonging to the sequence-type-258 lineage. Currently, KPC-2 and KPC-3 variants are the most frequently reported among the nine different variants (KPC-2-KPC-10). MBLs belong to class B, including Verona integrin-encoded MBL (VIM), IMP, and NDM (New Delhi MBL). IMP was first demonstrated in Japan in *Serratia marcescens*. In 2001, in Greece, VIM-1 was identified in *Escherichia coli* from a hospitalized patient, and rapidly spread among *K. pneumoniae*, becoming endemic. Class D carbapenemase "OXA-48", reported in *K. pneumoniae* isolates from Turkey is remotely related to oxacillinase, which hydrolyzes carbapenems and penicillins, but not expanded-spectrum cephalosporins (< 46 % amino acid identity). Later, it spread to other Mediterranean countries and caused some outbreaks in northern European countries. Over the past 15 years, the rate of carbapenem resistance among *K. pneumoniae* has dramatically increased globally. Data from the EARS-Net database revealed that during 2010, the rates of CR-KP ranged from 0.2 % in Germany to 59.5 % in Greece, with higher rates generally demonstrated in the southern European countries. Italy, a southern European country ranked the third with a CR-KP rate of 15.8 %.

Among hospitalized patients, acquisition of CR-KP has been related to ICU stay, prior antibiotic exposure to different classes of antibiotics including carbapenems, cephalosporins, fluoroquinolones, and glycopeptides, severity of underlying illness, and poor functional status. In a previous prospective surveillance study of 299 patients hospitalized in a medical-surgical ICU revealed that 7 % were colonized at admission and 27 % acquired CR-KP during ICU stay. A previous study investigated the risk factors for CR-KP infection among 464 patients known to be rectally colonized, revealed that 42 (9 %) subsequently developed CR-KP infection, that was related to the following

risk factors: diabetes mellitus, previous invasive procedure, tracheostomy, urinary catheterization, prior exposure to an antipseudomonal penicillin, and solid tumor.

A previous study showed that the mortality was up to 50 % for the gentamicin-tigecycline combination therapy, up to 64 % for colistin-tigecycline combination regimen, and up to 67 % for colistin-carbapenem regimen. Among the monotherapy-treated patients, mortality was up to 57 % for colistin and up to 80 % for tigecycline. A previous study on treatment outcomes in CR-KP bacteremia or septicemia revealed that the 90-day readmission rate for hospitalized survivors was 72 % and time to active therapy was not significantly different between survivors and non-survivors. The hospital mortality was similar regardless of therapy choice. CR-KP bloodstream infections can occur in patients with chronic and acute illness.

In conclusions, the diverse genetic mechanisms harbored by these carbapenem-resistant *K. pneumoniae* can facilitates its spread and complicates its identification. Combination antimicrobial treatment may be optimal option for patients with severe infections and severe illness. The correlation between microbiological trends with host characteristics and clinical factors will provide a better insight of pathogen control and rational treatment strategies. Nevertheless, well-designed randomized studies of specific populations are needed for further clarification of this topic.

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